In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 17-255V
Filed: June 12, 2023
PUBLISHED

SYLVESTER WILLIAMS,

Petitioner,

v.

SECRETARY OF HEALTH AND HUMAN SERVICES,

Respondent.

Special Master Horner

Joseph Alexander Vuckovich, Maglio Christopher & Toale, PA, Washington, DC, for petitioner.
Rachelle Bishop, U.S. Department of Justice, Washington, DC, for respondent.

DECISION[1]

On February 22, 2017, petitioner, Sylvester Williams, filed a petition under the National Childhood Vaccine Injury Act, 42 U.S.C. § 300aa-10-34 (2012), alleging that a Recombivax hepatitis B vaccine he received on June 30, 2015, caused him to suffer autoimmune hepatitis ("AIH"). For the reasons set forth below, I conclude that petitioner is *not* entitled to an award of compensation.

I. Applicable Statutory Scheme

Under the National Vaccine Injury Compensation Program, compensation awards are made to individuals who have suffered injuries after receiving vaccines. In general, to gain an award, a petitioner must make several factual demonstrations, including showing that an individual received a vaccination covered by the statute;

[1] Because this document contains a reasoned explanation for the action taken in this case, it must be made publicly accessible and will be posted on the United States Court of Federal Claims' website, and/or at https://www.govinfo.gov/app/collection/uscourts/national/cofc, in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2018) (Federal Management and Promotion of Electronic Government Services). **This means the document will be available to anyone with access to the internet.** In accordance with Vaccine Rule 18(b), Petitioner has 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, I agree that the identified material fits within this definition, I will redact such material from public access.

received it in the United States; suffered a serious, long-standing injury; and has received no previous award or settlement on account of the injury. Finally—and the key question in most cases under the Program—the petitioner must also establish a *causal link* between the vaccination and the injury. In some cases, the petitioner may simply demonstrate the occurrence of what has been called a "Table Injury." That is, it may be shown that the vaccine recipient suffered an injury of the type enumerated in the "Vaccine Injury Table," corresponding to the vaccination in question, within an applicable timeframe following the vaccination also specified in the Table. If so, the Table Injury is presumed to have been caused by the vaccination, and the petitioner is automatically entitled to compensation, unless it is affirmatively shown that the injury was caused by some factor other than the vaccination. § 300aa-13(a)(1)(A); § 300 aa-11(c)(1)(C)(i); § 300aa-14(a); § 300aa-13(a)(1)(B).

In many cases, however, the vaccine recipient may have suffered an injury *not* of the type covered in the Vaccine Injury Table. In such instances, an alternative means exists to demonstrate entitlement to a Program award. That is, the petitioner may gain an award by showing that the recipient's injury was "caused-in-fact" by the vaccination in question. § 300aa-13(a)(1)(B); § 300aa-11(c)(1)(C)(ii). In such a situation the presumptions available under the Vaccine Injury Table are inoperative. The burden is on the petitioner to introduce evidence demonstrating that the vaccination actually caused the injury in question. *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005); *Hines v. Sec'y of Health & Human Servs.*, 940 F.2d 1518, 1525 (Fed. Cir. 1991). Because autoimmune hepatitis is not listed as an injury on the Vaccine Injury Table, petitioner must satisfy this burden of proof.

The showing of "causation-in-fact" must satisfy the "preponderance of the evidence" standard, the same standard ordinarily used in tort litigation. § 300aa-13(a)(1)(A); *see also Althen*, 418 F.3d at 1279; *Hines*, 940 F.2d at 1525. Under that standard, the petitioner must show that it is "more probable than not" that the vaccination was the cause of the injury. *Althen*, 418 F.3d at 1279. The petitioner need not show that the vaccination was the sole cause of the injury or condition, but must demonstrate that the vaccination was at least a "substantial factor" in causing the condition, and was a "but for" cause. *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999). Thus, the petitioner must supply "proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury;" the logical sequence must be supported by "reputable medical or scientific explanation, *i.e.*, evidence in the form of scientific studies or expert medical testimony." *Althen*, 418 F.3d at 1278; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). A petitioner may not receive a Vaccine Program award based solely on his or her assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. § 300aa-13(a)(1).

In what has become the predominant framing of this burden of proof, the *Althen* court described the "causation-in-fact" standard, as follows:

> Concisely stated, [petitioner's] burden is to show by preponderant evidence that the vaccination brought about her injury by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of proximate temporal relationship between vaccination and injury. If [petitioner] satisfies this burden, she is entitled to recover unless the [government] shows, also by a preponderance of the evidence, that the injury was in fact caused by factors unrelated to the vaccine.

Althen, 418 F.3d at 1278 (citations omitted). The *Althen* court noted that a petitioner need not necessarily supply evidence from medical literature supporting petitioner's causation contention, so long as the petitioner supplies the medical opinion of an expert. *Id*. at 1279-80. That expert's opinion must be based upon "sound and reliable" scientific explanation. *Boatmon v. Sec'y of Health & Human Servs.*, 941 F.3d 1351, 1359 (Fed. Cir. 2019) (quoting *Knudsen v. Sec'y of Health & Human Servs*., 35 F.3d 543, 548-49 (Fed. Cir. 1994)). The *Althen* court also indicated that, in finding causation, a Program factfinder may rely upon "circumstantial evidence," which the court found to be consistent with the "system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." 418 F.3d at 1280.

II. Procedural History

This case was initially assigned to Special Master Millman. (ECF No. 4.) Petitioner filed medical records marked as Exhibits 1-8 on March 7, 2017. (ECF No. 7.) Respondent filed a Rule 4 Report recommending against compensation on September 28, 2017. (ECF No. 12.) Respondent asserted that without an expert report, petitioner's medical records were inadequate to support causation-in-fact. (*Id*. at 8-10.)

Petitioner filed additional medical records marked as Exhibits 9-13 on November 17, 2017. (ECF No. 18.) On January 30, 2018, petitioner filed an expert report and supporting literature of immunologist Eric Gershwin, M.D. (ECF Nos. 24-30; Exs. 14-73.) Petitioner subsequently filed further medical records marked as Exhibits 74-77 between March and April of 2018.[2] (ECF Nos. 33-34.)

Thereafter, respondent sent a correspondence on behalf of the parties to one of petitioner's treating physicians, Dr. Shiffman, on May 2, 2018, seeking clarification of his records. (ECF No. 35.) Specifically, Dr. Shiffman's records contained conflicting notations regarding whether petitioner had serologic evidence of previous exposure to hepatitis B and whether Dr. Shiffman recommended petitioner be vaccinated against hepatitis B. (ECF No. 32.) Respondent filed a letter by Dr. Shiffman marked as Exhibit A on July 23, 2018. (ECF No. 39.) In this letter, Dr. Shiffman indicates that vaccination against hepatitis B is an appropriate treatment for petitioner, but that he did have

[2] Due to a filing error, two of these articles were not ultimately filed until June 9, 2023, shortly before issuance of this decision. (ECF No. 109; Exs. 138-139.) Although not ultimately discussed, I have reviewed these late filed articles.

serologic evidence of a prior hepatitis B vaccination, meaning no further hepatitis B immunization was necessary. (Ex. A, p. 2.)

Respondent subsequently filed two expert reports on October 5, 2018. (ECF Nos. 41-47.) Respondent filed a report by immunologist Andrew MacGinnitie, M.D., Ph.D., (Ex. B) with supporting literature marked as Tabs B1-23, and by hepatologist Craig Lammert, M.D., (Ex. D) with supporting literature marked as Tabs D1-26.[3] Curricula vitae were marked Exhibits C and E respectively. (*Id*.) Petitioner filed a responsive expert report by Dr. Gershwin with supporting literature on May 30, 2019. (ECF Nos. 54-55; Exs. 78-95.)

The case was reassigned to the undersigned on June 6, 2019. (ECF Nos. 56-57.) Thereafter, the parties continued to exchange expert reports. Respondent filed supplemental reports by Drs. Lammert and MacGinnitie on October 17, 2019. (ECF No. 61; Exs. F-G.) Petitioner then filed updated medical records (Exhibits 96-98), a further report by Dr. Gershwin (Exs. 99-104), and a report by hepatologist Robert Gish, M.D. (Exs. 105-118). (ECF Nos. 65-67.) Respondent filed further reports by Drs. Lammert and MacGinnitie on November 2, 2020, marked as Exhibits H and I. (ECF Nos. 71-73.) Petitioner filed updated medical records on January 5, 2021, marked as Exhibits 119-121, and a supplemental report by Dr. Gish on March 31, 2021 (Ex. 122-128). (ECF Nos. 75, 79.) Respondent filed a further report by Dr. Lammert in response. (ECF No. 82; Ex. J.)

I held a status conference with the parties on October 21, 2021. (ECF No. 87.) I explained that I believed the expert presentations appeared complete. I advised that the issue of onset appeared to present a close question that could potentially warrant a hearing, but that the question of vaccine causation "is more a matter of my weighing of the evidence than a need for further expert explanation." (*Id*. at 1.) I indicated that if petitioner objected to proceeding with a ruling on the written record pursuant to Vaccine Rule 8(d), I would provide him an opportunity to argue in favor of an entitlement hearing before determining how to proceed. (*Id*.) Thereafter, petitioner requested that the case be resolved based on written submissions. (ECF No. 88.)

Petitioner subsequently filed further updated medical records as Exhibit 135, a final report by Dr. Gershwin as Exhibit 136, and a declaration marked as Exhibit 137.[4] (ECF Nos. 96, 101.) Petitioner filed a motion for a ruling on the record on April 5, 2022. (ECF No. 98.) Respondent filed his response on July 11, 2022, accompanied by a final report by Dr. MacGinnitie. (ECF Nos. 103-04; Ex. K.) Additionally, respondent filed a motion for leave to file additional medical literature. (ECF No. 105.) Petitioner filed a response opposing respondent's motion for leave to file on July 25, 2022, and his reply

[3] Exhibit D, Tab 18, was actually filed at a later date. (ECF No. 53.)

[4] The declaration is limited to confirming his receipt of a covered vaccine within the United States, the fact that his alleged injury lasted for longer than six months, and that he has not received any award or settlement of a civil action for damages related to his alleged injury. (Ex. 137.)

supporting his motion for a ruling on the record on August 10, 2022. (ECF Nos. 106-107.)

This case is now ripe for resolution. I have concluded that the parties have had a full and fair opportunity to develop the record and that it is appropriate to resolve this case without an entitlement hearing. S*ee Kreizenbeck v. Sec'y of Health & Human Servs*., 945 F.3d 1362, 1366 (Fed. Cir. 2020) (citing *Simanski v. Sec'y of Health & Human Servs*., 671 F.3d 1368, 1385 (Fed. Cir. 2012); *Jay v. Sec'y of Health & Human Servs.*, 998 F.2d 979, 983 (Fed. Cir. 1993.)); *see also* Vaccine Rule 8(d); Vaccine Rule 3(b)(2).

III. Respondent's Motion for Leave to File Additional Literature

During the October 21, 2021, status conference, petitioner requested that he be permitted to file a final clarifying report by Dr. Gershwin. (ECF No. 87.) I allowed petitioner to file the requested report and advised the parties to address "whether the wild hepatitis B [virus] can be associated with autoimmune hepatitis and the significance that has to Dr. Gershwin's molecular mimicry theory." (*Id* at 2.) However, I specified that petitioner was not permitted to file additional literature absent leave to do so. (*Id*.)

In his subsequently filed report, Dr. Gershwin asserted that he can reasonably link the hepatitis B virus to AIH circumstantially, but acknowledged that there is a lack of epidemiologic data to support an association. (Ex. 136, p. 1.) In particular, Dr. Gershwin noted that the previously filed paper by Maya et al., of which he is a co-author, "concluded that there is not sufficient data to determine whether or not the Hepatitis B virus is a pathogenic factor for AIH." (*Id*. (citing Maya et al., *Hepatitis B Virus (HBV) and Autoimmune Disease*, 34 CLINICAL REVIEWS ALLERGY & IMMUNOLOGY 85 (2008) (Ex. 115)).) In presenting his proposed circumstantial case, Dr. Gershwin asserted, *inter alia*, that adverse events following the Covid-19 vaccination (specifically autoimmune myocarditis and thrombosis) support his overall theory. (*Id*. at 2.) In response, Dr. MacGinnitie's final report further asserts that the wild hepatitis B virus is *not* associated with AIH, citing four additional studies in support of that point. (Ex. K.) Dr. MacGinnitie also cited two studies he indicates show the conditions referenced by Dr. Gershwin have a high correlation to Covid-19 infection. (*Id*.)

Respondent moved for leave to file the six articles cited in Dr. MacGinnitie's final report. (ECF No. 105.) Respondent asserts the articles are directly responsive to the undersigned's prompt and rebut Dr. Gershwin's unsupported statements in his own final report. (*Id*. at 1.) Petitioner argues that respondent has not shown good cause for the requested filings, stressing in particular that it would violate the principle of receiving evidence "in fundamental fairness to both parties" if the undersigned forbade petitioner from filing additional literature while allowing respondent to then file literature in rebuttal. (ECF No. 106.)

Regardless of the equities of any additional filings generally, I am not persuaded by respondent's contention that this proposed filing is reasonably necessary. After I

provided the parties an opportunity to address whether Hepatitis B virus is associated with AIH, petitioner's expert acknowledged there is not epidemiologic evidence to support such an association. Respondent's expert agrees. Additional literature addressing this undisputed point would be merely cumulative and is therefore unnecessary. Dr. Gershwin's brief reference to Covid-19 vaccine adverse events is not helpful in resolving this case and need not be rebutted. Accordingly, respondent's motion for leave to file additional literature is DENIED.

IV. Factual History

a. Pre-vaccination

Petitioner was born in 1980, making him 34 years old at the time of the 2015 hepatitis B vaccination at issue in this case. Prior to that vaccination, petitioner had a history of kidney stones, low back pain, obesity, and electrocution. (Ex. 2, pp. 6, 10, 13, 22; Ex. 6, p. 677; Ex. 7, p. 3.) Between late 2010 and early 2015, petitioner was evaluated at the emergency department on eleven separate occasions. This appears to have been petitioner's primary means of accessing healthcare as no primary care records have been filed for this period.

On November 8, 2010, he was seen for myalgia, cough, diarrhea, and scratchy throat. (Ex. 7, p. 9.) A viral syndrome was suspected. (*Id.* at 11.) On December 16, 2010, he was seen for several weeks of intermittent nausea and diarrhea. (Ex. 7, p. 17.) Gastroenteritis was suspected. (*Id*. at 21.) On October 13, 2011, he was seen for urethritis. (Ex. 2, pp. 31-37.) On June 18, 2012, he presented with a complaint of dizziness. (Ex. 7, p. 34.) On March 30, 2013, he presented with flank pain. (Ex. 2, pp. 28-30.) He presented on May 18, 2014, with left lower back pain attributed to kidney stones. (Ex. 2, pp. 10-13.) On September 14, 2014, he presented with an earache. (Ex. 6, p. 521.) On October 13, 2014, he presented for ear pain with bleeding. (Ex. 6, p. 471.) On November 6, 2014, he presented for foot swelling with numbness. (Ex. 6, p. 408.) On February 15, 2015, he presented for abdominal cramps and diarrhea. (*Id*. at 333.) At that time his bloodwork revealed elevated ALT[5] of 119 (IU/L) against a

[5] "ALT" refers to alanine transaminase, which is an enzyme of the transferase class that catalyzes the reversible transfer of an amino group from alanine to α-ketoglutarate to form glutamate and pyruvate, with pyridoxal phosphate as a cofactor. Serum enzyme activity (SGPT) is greatly increased in liver disease and also elevated in infectious mononucleosis. *Alanine transaminase*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=1509 (last visited May 30, 2023).

reference range of 10-50 (IU/L). (*Id*. at 336.) However, his AST,[6] bilirubin,[7] and albumin[8] were normal. (*Id*.) He was diagnosed with a viral syndrome and volume depletion. (*Id*. at 337.)

On June 30, 2015, petitioner presented to Walmart Pharmacy where he was administered a Boostrix tetanus-diphtheria-acellular pertussis ("Tdap") vaccine[9] and the Recombivax hepatitis B vaccine at issue in this case. (Ex. 1, p. 10.)

b. Post-vaccination

Twenty-eight days post-vaccination, petitioner presented to the emergency department with complaints of left flank pain, yellowing of the sclerae (*i.e.,* the whites of the eyes), and dark urine. (Ex. 6, pp. 229, 235.) He reported that his flank pain had begun about two to three days prior and the yellowing of his eyes the day of his presentation. (*Id*.) Liver enzymes were elevated, with ALT of greater than 997 U/L and AST of 585/UL.[10] (*Id*. at 237.) Albumin was not noted to be high at 3.8 gm/dL, but total bilirubin was marked as high at 6.2 mg/dL. (*Id*.) An abdominal and pelvic CT scan was performed. (*Id*. at 238.) Some small non-obstructing kidney stones were detected; however, petitioner's liver was noted to be unremarkable. (*Id*. at 238-39.) Petitioner

[6] "AST refers to aspartate transaminase, which is an enzyme of the transferase class that catalyzes the reversible transfer of an amino group from aspartate to α-ketoglutarate to form glutamate and oxaloacetate, with pyridoxal phosphate required as a cofactor. The enzyme is present in most eukaryotic cells, occurring as distinct isozymes in mitochondria and cytosol. Both isozymes participate in the malate-aspartate shuttle, and in the liver the reaction transfers excess metabolic nitrogen into aspartate for disposal via the urea cycle. The serum level of aspartate transaminase (SGOT) and that of other transaminases are frequently elevated in a variety of disorders causing tissue damage (e.g., myocardial infarction). *Aspartate transaminase*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=4466 (last visited May 30, 2023).

[7] Bilirubin is a yellow bile pigment that is a breakdown product of heme mainly formed from the degradation of erythrocyte hemoglobin in reticuloendothelial cells; it is also formed by breakdown of other heme pigments, such as cytochromes. Bilirubin normally circulates in plasma as a complex with albumin, and is taken up by the liver cells and conjugated to form water-soluble bilirubin diglucuronide for excretion in the bile. High concentrations of bilirubin may result in jaundice. *Bilirubin*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=6102&searchterm=bilirubin (last visited May 30, 2023).

[8] Serum albumin is the major plasma protein responsible for much of the plasma colloidal osmotic pressure and serves as a transport protein for large organic anions such as fatty acids, bilirubin, and many drugs; it also carries hormones such as cortisol and thyroxine when their specific binding globulins are saturated. It is synthesized in the liver. Decreased serum albumin (hypoalbuminemia) occurs in protein malnutrition, active inflammation, and serious hepatic and renal disease. *Albumin*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=1550&searchterm=albumin (last visited May 30, 2023).

[9] Petitioner has not alleged the Tdap vaccine caused or contributed to his injury.

[10] The results for this panel were marked with a notation identifying which results were interpreted as high, but no reference range was provided. (Ex. 6, p. 237.)

was initially diagnosed with jaundice, but with recommended follow up for suspected viral hepatitis. (*Id*. at 241.)

Petitioner again sought care from a different emergency department on August 1, 2015. (Ex. 7, p. 49.) Petitioner noted the fact that he had recently been vaccinated against hepatitis B. He had yellowed eyes, but denied any abdominal pain. (*Id*.) Liver enzymes were again elevated, with ALT at 1,222 U/L (reference range 12-78 U/L) and AST at 677 U/L (reference range 15-37 U/L). (*Id*. at 52.) Albumin was low at 3.3 g/dL (reference range 3.4-5.0 g/dL) and total bilirubin was high at 7.4 mg/dL (reference range 0.2-1.0 mg/dL). (*Id*.) An abdominal ultrasound found some gallbladder abnormalities, but the liver was unremarkable. (*Id*. at 53.) He was diagnosed with jaundice, elevated liver function tests, and a urinary tract infection. (*Id*. at 54-56.)

On August 5, 2015, petitioner was evaluated by gastroenterologist Zahid Rashid, M.D. (Ex. 4, p. 195; Ex. 8, pp. 2-3.) Petitioner denied having pain, except with solid foods. He reported history of hepatitis B vaccination. (Ex. 8 at 2.) Dr. Rashid diagnosed jaundice, abdominal pain, abnormal serum enzyme levels, weight loss, and nausea. However, he was concerned petitioner may have autoimmune hepatitis and ordered further testing. (*Id.* at 2-3.) More lab work was done the next day, which continued to show elevated ALT, AST, and bilirubin, though ALT was improving. (*Id.* at 4, 8.) Petitioner returned to Dr. Rashid on August 10, 2015, for follow up, though he had no complaints as of that day. (*Id*. at 8.) Dr. Rashid diagnosed "unspecified hepatitis" and ordered a liver biopsy to determine whether petitioner had autoimmune hepatitis. (*Id*. at 9.)

On August 19, 2015, a liver biopsy was performed. (Ex. 4, p. 228.) The reviewing pathologist indicated the core biopsy samples were "good quality specimens." The results showed "considerable inflammation." No steatohepatitis (*i.e*., nonalcoholic fatty liver disease) was observed. The diagnosis was "chronic hepatitis, with moderate necroinflammatory activity (Grade 3), and slight fibrous portal expansion (Stage 1)." Additionally, [t]he presence of a component of eosinophils and plasma cells suggests the possibility of a non-viral origin or a multifactorial origin. Serologic testing for possible autoimmune or hepatitis is suggested, along with the evaluation of drug history." (*Id.*)

Thereafter, Dr. Rashid referred petitioner to hepatology specialist Mitchell L. Shiffman, M.D. Petitioner presented to Dr. Shiffman on August 21, 2015. (Ex. 5, p. 4.) Lab results from August 21, 2015, continued to show elevated ALT, AST, and bilirubin. (*Id*. at 6.) Dr. Shiffman noted petitioner's liver ultrasound showed a "normal appearing liver." (*Id*.) He indicated petitioner had "acute and marked elevation" in liver transaminases, but normal liver function and "[b]ased upon laboratory studies and imaging the patient does not appear to have significant liver disease or cirrhosis."[11] (*Id*.

[11] Petitioner characterizes Dr. Shiffman's August 21, 2015, record as indicating that elevated liver enzymes began in July of 2015. (ECF No. 98-1, pp. 11-12.) Petitioner suggests that this is significant because petitioner had elevated liver enzymes in February of 2015. (*Id*. citing Ex. 6, p. 336). This would seem to allude to the disagreement between petitioner's hepatology expert, Dr. Gish, and respondent's hepatology expert, Dr. Lammert, regarding whether petitioner's February 2015 lab work demonstrated a true finding. Dr. Gish opines that elevated ALT without elevated AST and bilirubin should not be credited.

at 7.) Dr. Shiffman noted he did not yet have access to the liver biopsy. (*Id*.) He noted that the need for vaccination against hepatitis A and B would be assessed based on serology and that the patient had no contraindication for any current medications. (*Id*.) Dr. Shiffman felt the most likely causes for petitioner's abnormal liver chemistry included immune liver disorders, but intended to perform additional testing and review the prior biopsy. (*Id*.)

Petitioner returned to Dr. Shiffman on August 27, 2015. (Ex. 5, pp. 31-40.) By this time, Dr. Shiffman had reviewed the liver biopsy and concluded that it "demonstrates severe inflammation with piecemeal necrosis consistent with an autoimmune hepatitis." (*Id*. at 31.) Dr. Shiffman personally reviewed the biopsy slides. He felt the specimens were "fragmented but adequate." He noted "[s]evere aggressive inflammation" and suggested "[t]he degree of fibrosis may be underestimated by fragmentation." (*Id*. at 34.) AST, ALT, and bilirubin continued to be elevated as of August 26, 2015. (*Id*. 33.) The lab report indicates that serology was negative for hepatitis B surface antigen, though a separate notation indicates it was positive. (*Id*. at 3-34.) Dr. Shiffman diagnosed autoimmune hepatitis and started petitioner on prednisone. Vaccination against hepatitis A and B was recommended based on the reported serology.[12] (*Id*. at 34-35.)

Although petitioner has had an extensive subsequent course of treatment for his autoimmune hepatitis, it is not necessary to review that history given that petitioner's diagnosis is not disputed. Additionally, none of the subsequent records include any treating physician opinions with respect to either the initial onset of petitioner's condition or whether it may have been vaccine caused. Nor is further review of the subsequent medical history necessary to understand the bases of the experts' opinions.

V. Expert Opinions

Each party has presented an expert opinion from an immunologist as well as a hepatologist. At first, petitioner relied exclusively on Dr. Gershwin (immunologist) to support his claim. However, after respondent retained both a hepatology expert (Dr. Lammert) and an immunology expert (Dr. MacGinnitie) to respond, petitioner eventually retained Dr. Gish (hepatology). Because the resulting reports of all four experts are

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(Ex. 105, p. 9.) Thus, petitioner seems to be implying that Dr. Shiffman's August 21, 2015, record should be viewed as discounting the significance of the February 2015 result, thereby effectively endorsing Dr. Gish's opinion over Dr. Lammert's competing view. Importantly, however, this record explicitly confirms that "[s]erologic evaluation for markers of chronic liver disease are not available to me." (Ex. 5, p. 4.) Dr. Shiffman indicates that he reviewed records provided by the referring physician. (*Id*.) In turn, Dr. Rashid's records indicate awareness of petitioner's prior July and August emergency encounters, but offer no indication Dr. Rashid reviewed earlier treatment records. (Ex. 8, pp. 2-3.) There is therefore little to no basis for concluding that Dr. Shiffman was opining as to the significance of the February 2015 result.

[12] As explained in the procedural history, Dr. Shiffman has provided a letter (Exhibit A) explaining that the recommendation for a hepatitis B vaccine was an error. He indicates that as of the August 27, 2015, encounter, the test for hepatitis B surface antibodies had not yet resulted and should not have been recorded as negative. Dr. Shiffman indicates the record is corrected as of January 19, 2018.

numerous, overlapping, and effectively "in conversation," the most effective way to describe the reports is to divide them first by topic and then by direct exchange between the various experts. What follows is a summary of the experts' separate exchanges on general vaccine causation followed by an additional summary of the exchanges regarding petitioner's own clinical history.

a. Opinions regarding general causation

There is no debate in this case that AIH is, as the name indicates, an autoimmune condition. Moreover, there is also no debate that the etiology of the condition is unknown apart from the fact that it likely involves a combination of genetic susceptibility and an environmental stimulus. However, the experts differ greatly on whether there is sufficient evidence to further hypothesize that the hepatitis B vaccine may act as that stimulus.

1. Dr. Gershwin's first report[13]

Dr. Gershwin explains that the true incidence of autoimmune hepatitis is unclear, but that it is generally estimated at about 1 out of 100,000 per year. (Ex. 14, p. 2.) Thus, he contends it is difficult to assess epidemiologically. Dr. Gershwin's report quotes multiple pieces of literature that confirm the etiology of AIH remains unknown (*Id*. at 3, 6); however, he indicates that it is well established that both genetic predisposition and environmental factors play a role in its pathogenesis. (*Id*. at 2.) For example, prior studies have shown specific populations to demonstrate autoimmune hepatitis following viral infections and it can also be drug induced. (*Id*.)

Dr. Gershwin opines that AIH is likely initiated by innate immunity which is then followed by an adaptive immune response leading to autoimmunity. (*Id.*) Dr. Gershwin quotes at length a review paper by Olivier, et al., which indicates, *inter alia*

> T-cell mediated cytotoxicity appears to be the central mechanism responsible for the hepatic damage, and a role for autoantibodies in the pathogenesis of the disease has not yet been identified. In other words, in spite of diagnostic criteria that rely on circulating autoantibodies, AIH is considered a cell-mediated autoimmune disease.

[13] Dr. Gershwin is currently a distinguished professor of medicine and the Jack and Donald Chia Professor of Medicine in the Rheumatology/Allergy and Clinical Immunology division of the University of California at Davis, where he previously served as chairperson of the Graduate Group in Immunology. (Ex. 15, p. 1.) Dr. Gershwin received his bachelor's degree from Syracuse University and his master's degree from the Centre for Astrophysics and Supercomputing. (*Id*.) He received his Doctor of Medicine from Stanford University and is currently licensed to practice medicine in California. (*Id.* at 1-2.) Dr. Gershwin is board certified in Internal Medicine with a subspecialty in Rheumatology and in Allergy and Clinical Immunology. (*Id.* at 1-2.) In addition, he has published 71 books and monographs and 234 peer-reviewed articles. (*Id.* at 13-126.)

(*Id*. at 3 (internal citations omitted) (quoting Oliveira et al., *Autoimmune Hepatitis, HLA and Extended Haplotypes*, 10 AUTOIMMUNITY REVIEWS 189, 190 (2011) (Ex. 21, p. 2)).)

Dr. Gershwin indicates that his own prior research shows that the liver is a lymphoid organ containing cells capable of both adaptive and innate immune responses. In particular, he stresses an animal model study that exposed mice to Con-A to produce an elevation of cytokines and, in turn, induction of AIH. (*Id*. at 4.) Thus, he opines that AIH is distinguished from other autoimmune conditions by the fact that it results from an immediate, T-cell mediated immune response. (*Id*.)

Dr. Gershwin quotes literature noting that AIH may be incited by various factors, including hepatitis infection and vaccination. (*Id*. at 6.) However, that same literature explains that

> Infectious agents like hepatitis viruses have often been mentioned as triggers of autoimmune diseases. Associations between hepatotropic viruses and autoimmune processes directed against the liver have been described, but there is no evidence of an etiologic role. Although [hepatitis C virus] has co-existed with AIH more than other hepatitis viruses, the strongest evidence is probably related to [hepatitis A virus] . . . AIH has been associated with immune intolerance to self-antigens combined with a failure of intrinsic homeostatic mechanisms that prevent a promiscuous immune response to those antigens. Probably multiple antigens can trigger autoimmune hepatitis . . . Several mechanisms have been postulated or have been confirmed to cause development of autoimmune disease. The first mechanism described is molecular mimicry. Antigenic determinants of vaccine contain a sequence of amino acids, sufficiently similar to a self-antigen, to produce cross-reactivity with the formation of autoantibodies and/or activation of specific T cells . . .

(*Id*. at 6 (quoting Van Gemeren et al, *Vaccine-related Autoimmune Hepatitis: The Same Disease as Idiopathic Autoimmune Hepatitis? Two Clinical Reports and Review*, 52 (2017) 18, 20 (Ex. 68, p. 4)).)

Based on all of this, Dr. Gershwin theorizes that petitioner's hepatitis B vaccine resulted in an organ-specific innate inflammatory response that resulted in a loss of self-tolerance, *i.e.,* the vaccine caused in an autoinflammatory condition affecting the liver. The innate immune response within the liver elicited a secondary adaptive immune response in which native liver antigens were altered by the autoinflammation to become "neoantigens." (*Id*. at 7.) Thus, Dr. Gershwin opines that petitioner's vaccine caused AIH via molecular mimicry at the T-cell level. (*Id*. at 7-8.)

2. Dr. MacGinnitie's[14] and Dr. Lammert's[15] first reports

Dr. MacGinnitie stresses that there is no epidemiologic association between hepatitis B vaccine and either AIH or autoimmunity generally. (Ex. B, p. 6.) Even as Dr. Gershwin asserts that AIH is thought to include an environmental component, Dr. MacGinnitie stresses that the cause of AIH remains unclear and that Dr. Gershwin's own research indicates no clear trigger is identified in the majority of cases. (*Id*. at 4.) Dr. MacGinnitie notes that Dr. Gershwin's primary reference connecting vaccinations to AIH is limited to six case reports. (*Id*. at 5.) Importantly, however, he notes that they are inadequate to evidence causality, especially, but not only, because all of the case reports included vaccination for hepatitis A while only two of the six included hepatitis B vaccination at all. (*Id*. at 5-6.)

Dr. MacGinnitie also raises several challenges to Dr. Gershwin's theory of causation. First, he notes that there is no evidence to support molecular mimicry between components of the hepatitis B vaccine and human liver tissue. (*Id*. at 4.) Second, he contests the applicability of the Con A mouse model to human disease. (*Id.* at 6-7.) And third, he explains that vaccines do not cause "an unusual degree of inflammation," contrasting response to vaccination in particular with the high-level cytokine response artificially induced in the Con A mouse model. (*Id*. at 4-5, 6-7.) Dr. MacGinnitie charges that Dr. Gershwin's theory is vague and unsupported. (*Id*. at 4.)

Dr. Lammert likewise opines that there is not sufficient literature to support the hepatitis B vaccine as a cause of AIH. (Ex. D, p. 2.) He stresses that vaccination against hepatitis A and B is the standard of care for AIH patients, which would not be the case if a vaccine reaction was a "strong possibility." (*Id*. at 6.) Dr. Lammert explains that AIH is a chronic, mostly T-cell mediated autoinflammatory disease. He stresses that the pathophysiology is not well understood, though he agrees with Dr. Gershwin that it likely involves genetic and environmental factors. (*Id*. at 6-7.)

[14] Dr. MacGinnitie is currently an attending physician in pediatrics allergy/immunology at Boston Children's Hospital. (Ex. C, p. 1.) He received his bachelor's degree from Yale and his Doctor of Medicine from the University of Chicago Pritzker School of Medicine, where he also received a Doctor of Philosophy in Pathology. (*Id.*) Dr. MacGinnitie is licensed to practice medicine in Massachusetts and has authored 35 peer-reviewed articles. (*Id.* at 10-14.)

[15] Dr. Lammert is currently an Assistant Professor of Medicine at the Indiana University School of Medicine. (Ex. E, p. 1.) He received his bachelor's degree from Purdue University and his master's degree from Indiana University-Purdue University Indianapolis. (*Id.*) Dr. Lammert received his Doctor of Medicine from Indiana University School of Medicine and completed his residency at Emory University. (*Id.*) He was licensed to practice medicine in Indiana until 2019. (*Id.*) Dr. Lammert is a member of the American Association for the Study of Liver Diseases, the American Gastroenterology Association, the American College of Physicians, and the International Autoimmune Hepatitis Group. He has authored 14 peer-reviewed articles. (*Id.* at 5-6.)

However, he indicates the available evidence does not support the hepatitis B vaccination as a cause of autoimmunity generally or AIH specifically. (*Id*. at 7.)

3. Dr. Gershwin's second report

In response to Dr. MacGinnitie's report, Dr. Gershwin agrees that "the etiology of autoimmune hepatitis remains enigmatic." (Ex. 78, p. 2.) He also acknowledges that his theory cannot be epidemiologically supported, though he again stresses this is due to the rarity of the condition. (*Id*. at 3.)

With respect to molecular mimicry, however, he does not agree with Dr. MacGinnitie's opinion that the hepatitis B protein must be expressed in the human liver for autoimmunity to occur. (*Id*. at 2.) Dr. Gershwin cites his own prior publication with regard to general principles of molecular mimicry and indicates that "[i]n this case, the original antigenic target does not need to be structurally similar to the antigen targeted after somatic hypermutations, in contrast to autoantibodies generated by the mechanism referred to as molecular mimicry." (Ex. 78, pp. 1-2 (citing Rojas et al., *Molecular Mimicry and Autoimmunity*, 95 J. OF AUTOIMMUNITY 100 (2018) (Ex. 80)).)

Dr. Gershwin agrees with Dr. MacGinnitie's assertion that vaccines do not represent powerful or unusual immune stimuli, but effectively stresses the need to account for outliers. (*Id*. at 2-3.) With respect to his reliance on animal models, he indicates that:

> Animal models are important and I cite discussion of one animal model to illustrate the principle. However, there are nearly 20 proposed animal models of autoimmune hepatitis and virtually all of them are different from each other. They illustrate that it is virtually impossible to design a mouse model for AIH and further illustrate that multiple immune pathways can be involved in the generation of local inflammation and ultimately an autoimmune attack on the liver. Hence, my responses are not based on one animal model, but rather the proof of principles involved in AIH.

(*Id*. at 3 (internal citation omitted).)

4. Dr. MacGinnitie's and Dr. Lammert's second reports

Dr. MacGinnitie asserts that Dr. Gershwin's suggestion that homology is not required for molecular mimicry is contradicted by his own citation to Rojas, et al. (*supra* at Ex. 80.) Specifically, he notes that Dr. Gershwin has asserted that AIH is a T-cell mediated disease, which means molecular mimicry must occur at the peptide level given that T-cells operate by recognition of peptides of between 8-18 amino acids. He asserts that Rojas, et al., specifically states that "molecular mimicry . . . occur[s] when similarities between foreign and self-peptides favor an activation of autoreactive T or B cells" and that molecular mimicry requires "similarity between a host epitope and an

epitope of a microorganism or environmental agent." (Ex. F, p. 1 (quoting Rojas et al., *supra*, at Ex. 80, pp. 1, 4).) Further to this, he notes that homology cannot be equated with disease. (*Id*. at 2.) Dr. MacGinnitie charges that Dr. Gershwin's theory is untestable because "any exposure can potentially trigger autoimmunity (and presumably any type of autoimmunity) in the absence of predictable similarity between trigger and human protein." (*Id*.)

Dr. Lammert repeats his agreement that AIH likely involves both genetic and environmental factors, but strongly disagrees there is a basis for invoking molecular mimicry. (Ex. G, pp. 2-3.) Dr. Lammert also disputes there is evidence to support the hepatitis B vaccine as leading to an exacerbation of autoimmune disease. (*Id*. at 4-5.)

5. Dr. Gish's[16] and Dr. Lammert's additional exchanges on general causation

In his first report, Dr. Gish opines that "[b]ased on my clinical experience and my review of the literature, I am of the opinion that there is a linkage between vaccination and the development of AIH." (Ex. 105, p. 5.) Specifically, he endorses Dr. Gershwin's theory, which he characterizes as indicating that similarities between vaccine antigen and liver cells can lead to cross reaction.[17] (*Id*.) Dr. Gish opines that the linkage between hepatitis B infection and autoimmunity is established. (*Id*. (citing Maya et al., *supra*, at Ex. 115).) Thus, he opines there is a clear connection between Hepatitis B antigen and autoimmunity. He indicates that "I will defer to Dr. Gershwin's detailed review of the immunological issues and will simply note that there is nothing about Recombivax HB vaccine antigen or about the liver that would prevent this cross-reaction from occurring as it does for other antigens and other tissues and organs." (*Id*.) Further to this, Dr. Gish cites additional literature suggesting various autoimmune adverse reactions to the hepatitis B vaccine, including demyelinating conditions. (*Id*. (citing Bogdanos et al., *A Study of Molecular Mimicry and Immunological Cross-Reactivity Between Hepatitis B Surface Antigen and Myelin Mimics*, 12 Clinical Development in Immunology 217 (2005) (Ex. 108)).) Nonetheless, Dr. Gish also acknowledges that "[i]t is true that there are no cases of AIH following HBV immunization yet reported in the

[16] Dr. Gish is currently a principal physician at Robert G. Gish Consultant, LLC; a Clinical Professor of Medicine and Adjunct Professor of Clinical Medicine at the University of Nevada; a Clinical Professor at the University of Nevada Reno School of Medicine; and Medical Director of the Hepatitis B Foundation and the Asian Pacific Foundation. (Ex. 106, pp. 3-4.) Dr. Gish received his Doctor of Medicine from the University of Kansas and completed his residency at the University of California, San Diego. (*Id.* at 4-5.) He also completed a fellowship in Gastroenterology and Hepatology at the University of California, Los Angeles. (*Id.* at 5.) He is licensed to practice medicine in Arizona, California, and Nevada and is board certified in Internal Medicine, Gastroenterology, and CAQ Liver Transplantation. (*Id.* at 4.) Dr. Gish has authored 253 peer-reviewed articles. (*Id.* at 62-84.)

[17] Note that this description appears consistent with Dr. MacGinnitie's description of molecular mimicry and does not specifically account for Dr. Gershwin's reliance on somatic hypermutation leading to neoantigens within the liver to explain the lack of demonstrable homology.

literature . . .” (*Id*. at 6.) Instead, Dr. Gish posits that the association of hepatitis A vaccine with AIH specifically and the association of the hepatitis B vaccine with other forms of autoimmunity, “sets the stage” for a “possible” linkage between the hepatitis B vaccine and AIH “even though the viruses are different.” (*Id*.) Dr. Gish stresses the limitations of epidemiology in this context given the rarity of the condition. (*Id*. at 6-7.)

Dr. Lammert’s third report responds to Dr. Gish’s first. (Ex. I.) He credits Dr. Gish’s expertise in hepatology, but stresses that Dr. Gish is the medical director of the Hepatitis B Foundation, which “in stark conflict” with Dr. Gish’s proffered opinion maintains a public statement that there is “no confirmed evidence” that the hepatis B vaccine causes, *inter alia*, autoimmune disorders. (*Id*. at 1-2.) To the extent Dr. Gish cites his own prior clinical experience as support for his opinion, Dr. Lammert notes this assertion is not supported by any detail. Dr. Lammert suggests his own clinical experience is to the contrary. (*Id*. at 3.) In response to Dr. Gish’s extrapolation from autoimmunity more broadly, Dr. Lammert counters that the pathogenesis among various autoimmune condition is not the same. (*Id*. at 3-4.) Moreover, he disputes that a link between hepatitis A vaccine and AIH is established and, further, that any such link would provide guidance with respect to hepatitis B vaccine. (*Id*. at 4-5.) Dr. Lammert stresses that the vaccines themselves are very different, with the hepatitis A vaccine using inactivated hepatitis A virus and the hepatitis B vaccine using a hepatitis B surface antigen. (*Id*. at 5.)

In his second report, Dr. Gish explains that the position statement of the Hepatitis B Foundation is a broad statement based on epidemiology. It does not preclude offering the conclusion, based on peer-reviewed literature, that a rare individual can experience an adverse event undetected by epidemiology. (Ex. 122, pp. 1-2.) However, he appears to concede Dr. Lammert’s suggestion that he has no prior personal clinical experience with AIH he would causally attribute to vaccination. (*Id*. at 2-3.) Nonetheless, he does assert having prior clinical experience (five cases) of hepatitis B leading to AIH and therefore opines that hepatitis B infection can lead to autoimmune attack. (*Id*. at 5.) Dr. Gish acknowledges that each autoimmune condition has its own etiological features, but stresses that the conditions are classed together for a reason and suggests that Bogdanos, et al., demonstrates the hepatitis B antigen cross reacts with a number of different tissues. (*Supra,* at Ex. 108.) He suggests it would be “odd” if hepatitis B antigen could trigger other autoimmune conditions, but not AIH, given that they have common features. (*Id*. at 3.) Dr. Gish asserts the distinction raised by Dr. Lammert in vaccine formulation is “a distinction without a difference,” because both vaccines rely on a common mechanism of epitope spreading. (*Id*. at 4.)

Dr. Lammert’s final report seeks to rebut Dr. Gish by reiterating points previously addressed. (Ex. J.)

6. <u>Dr. Gershwin and Dr. MacGinnitie’s further exchanges on general causation</u>

In his third report, Dr. Gershwin responded to Dr. MacGinnitie's molecular mimicry criticism by suggesting that Dr. MacGinnitie requires too high of a bar for demonstration of molecular mimicry given the research resources required to actually identify and define epitopes. (Ex. 99, p. 1.) Dr. MacGinnitie agrees the process is difficult, but suggests that this still leaves Dr. Gershwin with a lack of supporting evidence and further suggests that the difficulty may be due at least in part to the rarity of molecular mimicry actually leading to autoimmune disease. (Ex. H, p. 1.)

In his fourth and final report, Dr. Gershwin responds to my request that the experts address the association, if any, between the wild hepatitis B virus and AIH. Dr. Gershwin acknowledges that there is not sufficient data to determine whether the hepatitis B virus causes AIH, but reasons that it can, given that it is liver-trophic. He states "[l]iver-trophic viruses such as HBV cause clinical symptoms in part by causing inflammation in parenchymal liver tissue, and all autoimmune diseases, including AIH, are diseases of inflammation. Therefore, it is logical to conclude that HBV can and does cause AIH in a small number of patients." (Ex. 136, p. 1.) Dr. Gershwin suggests the fact that the hepatitis B vaccine has been implicated in other autoimmune conditions such as MS, lupus, GBS, and rheumatic conditions, further supports the hypothesis given that mechanism of autoimmunity overlap. Given that, he reasons the wild hepatitis B virus can cause AIH. He further states:

> Vaccination works by presenting an antigen to the adaptive immune system in order to elicit an immune response that will be effective against the wild-type version of the antigen. This means that there will always be a very high degree of chemical and structural similarity between wild-type and vaccine antigen – otherwise, the vaccine will not serve its purpose of triggers protective adaptive immunity. If HBV can cause autoimmune complications including AIH then the most logical conclusion is that hepatitis B vaccine can also cause AIH and other autoimmune disorders.

(*Id*. at 2.)

In response to Dr. Gershwin's final report, Dr. MacGinnitie stresses the lack of epidemiologic support for the idea that the hepatitis B virus causes AIH. (Ex. K.) He also stresses that the hepatitis B vaccine contains only a single protein (hepatitis B surface antigen) whereas the wild virus has three additional proteins. Therefore, he suggests that, even if the wild virus was shown to induce molecular mimicry, it would not necessarily follow that the vaccine would as well. (*Id*. at 2.) Dr. MacGinnitie also disputes the logic that leads Dr. Gershwin to reason that the wild hepatitis B virus can cause AIH. He stresses that the fact that a disease causes tissue inflammation does not mean it can be said to cause an entirely different condition in the absence of evidence that it actually does so. He suggests that if hepatic inflammation were required to induce AIH, this would be an argument against vaccine causation given that

there is no evidence that an intramuscular vaccination would cause liver inflammation. (*Id*.)

b. Opinions regarding petitioner's clinical course

Turning from general causation to petitioner's own history, there is no debate in this case as to whether petitioner ultimately suffered AIH. However, the experts differ significantly on when he began to develop AIH and whether that supports vaccine-causation.

1. Dr. Gershwin's first report

Dr. Gershwin opines that petitioner developed clinical signs of AIH approximately one month following his hepatitis B vaccination, but likely suffered a subclinical course beginning shortly after vaccination. (Ex. 14, p. 4.) Especially because there were no other antecedent triggers, he opines the vaccination caused petitioner's AIH. (*Id*. at 8.) Dr. Gershwin stresses that he disagrees that it is appropriate to recommend immunization to someone during an acute phase of an autoimmune condition such as AIH. (*Id*.)

2. Dr. Lammert's first report

Dr. Lammert disagrees with Dr. Gershwin's assessment that petitioner was in reasonable health prior to the vaccination at issue. (Ex. D, p. 2.) He stresses that in the prior year petitioner presented to the emergency department many times with a "wide spectrum" of symptoms, including multiple visits for recurrent gastrointestinal complaints and flank pain. (*Id.* at 2-5.) Dr. Lammert explains that AIH has a heterogenous clinical presentation that can wax and wane, can include other organ systems, and often "is characterized by the presence of one or more non-specific symptoms." (*Id*. at 4.) As a result, diagnosis is often delayed. (*Id*.) Dr. Lammert indicates that the condition can be present for years before a progressive injury leads to visible symptoms and clinical evaluation and opines that petitioner's seven emergency department evaluations over the three years leading up to his diagnosis is consistent with evolving AIH. (*Id*. at 4-5.)

Dr. Lammert also stresses that four months prior to vaccination, petitioner presented for an evaluation on February 15, 2015, that included complaints of abdominal pain, weakness, and diarrhea. At that time, he had ALT of 119 (IU/L), which is over two times the upper normal limit for ALT. (*Id*. at 5 (citing Ex. 6, p. 336).) ALT is a surrogate marker for hepatic inflammation. Thus, Dr. Lammert finds this result highly significant in evaluating the overall course of petitioner's AIH. (*Id*.) Further to this, Dr. Lammert explains that petitioner's August 19, 2015, liver biopsy showed both grade 3 necroinflammatory activity and stage 1 fibrous portal expansion. (*Id*. at 5-6 (citing Ex. 4, p. 228).) According to Dr. Lammert, these findings are consistent with a chronic rather than acute course of AIH. In particular, he indicates that the finding of any fibrosis would require a period of subclinical disease prior to symptom presentation. (*Id*. at 6.)

Dr. Lammert does not find petitioner's clinical course to be consistent with either vaccine causation or significant aggravation of his AIH. (*Id*. at 8.)

3. Dr. Gershwin's second report and Dr. Lammert's responsive (second) report

Dr. Gershwin demurred with respect to Dr. Lammert's clinical assessment; however, he indicated that "even if Dr. Lammert's clinical assessment is correct, the medical evidence in this case still suggests that it is highly probable that any chronic, pre-existing AIH that Mr. Williams may have had was severely exacerbated by his vaccination." (Ex. 78, p. 4.) The exact basis for this statement is not indicated.

Dr. Lammert's second report largely reiterates his prior clinical assessment, adding that Dr. Gershwin's limited response does not address the points Dr. Lammert raised regarding an earlier onset of symptoms, elevated ALT predating the vaccination, and the specifics of petitioner's histology. (Ex. G, pp. 2-3.) Given his clinical assessment, Dr. Lammert stresses that "[i]n order to understand and assign disease risk to an environmental exposure, the onset of injury should not come BEORE the factor in question." (*Id*.) Dr. Lammert also disputes there is evidence to support the hepatitis B vaccine as leading to an exacerbation of autoimmune disease. (*Id*. at 4-5.)

4. Dr. Gish's first report

Dr. Gish challenges Dr. Lammert's assessment of petitioner's pre-vaccination history. He opines there is no evidence to support that petitioner had AIH or any other autoimmune condition prior to vaccination. He notes that the "non-specific" symptoms relied upon by Dr. Lammert are not strong evidence precisely because they are "non-specific." He notes that petitioner's pre-vaccination symptoms and his pattern of emergency department visits are also consistent with his obesity. (Ex. 105, p. 8.) He also indicates that many of petitioner's issues have other confirmed causes that do not implicate autoimmunity, including kidney stones and electroshock, and none of petitioner's symptoms are specific markers of any autoimmune condition. (*Id*. at 8-9.)

Dr. Gish opines that petitioner's single February 2015 finding of elevated ALT is not an appropriate basis to conclude petitioner was suffering AIH. (*Id*. at 9.) He explains that the ALT result is an enzyme test rather than a liver function test and liver enzymes can fluctuate rapidly due to a variety of factors. Additionally, petitioner's AST, another important liver enzyme that was measured at the same time, was within normal range. Dr. Gish suggests that elevated ALT and AST would together indicate liver inflammation. Additionally, he notes that petitioner did not have abnormal bilirubin levels until after his vaccination. He had normal bilirubin and albumin levels in February of 2016. Dr. Gish suggests bilirubin and albumin levels are a more accurate measure of liver function. (*Id*.) Given that only the ALT level was elevated, Dr. Gish opines this is more consistent with a fatty liver. (*Id*.)

Dr. Gish opines that a proper evaluation of the liver biopsy is not possible without directly reviewing the actual fixed tissue. (*Id*. at 9-10.) He agrees that petitioner had

stage 1 fibrosis, but opines that a chronic course of AIH as proposed by Dr. Lammert would result in stage 2 or greater fibrosis. (*Id*. at 10.) Because of his obesity, petitioner was at major risk for nonalcoholic fatty liver disease and that condition is a more likely explanation for the mild fibrosis seen in petitioner's case. (*Id*.) Dr. Gish opines that "I would attribute 20-25% of fibrosis to collapse and acute liver injury for AIH, with the 75-80% remainder attributable to pre-existing fatty liver disease." (*Id*. at 3.)

Dr. Gish indicates that:

> If pre-existing AIH is ruled out, then the temporal association between vaccination on June 30, 2015, and AIH symptom onset beginning less than a month later and continuing throughout the fall of 2015 is striking and certainly constitutes additional evidence of a causal relationship. The medical record does not indicate any infection or other environmental insult between the June 30, 2015, vaccination and the July 28, 2015, ED visit that would explain the patient's symptoms.

(*Id*. at 10.)

5. Dr. Lammert's third report (responding to Dr. Gish)

Dr. Lammert agrees that petitioner was obese, but does not agree his pattern of emergency department presentations is explained by that fact, noting he went to the emergency department more than would be typical. (Ex. I, p. 7.) He agrees that a single ALT elevation is not sufficient to diagnose AIH, but also explains that it is likewise insufficient to diagnose nonalcoholic fatty liver disease. (*Id*.) Furthermore, he stresses that petitioner's history includes no evidence of liver fat by either imaging or histology, which is a requirement for diagnosis of nonalcoholic fatty liver disease.[18] (*Id*.) Dr. Lammert is critical of Dr. Gish's suggestion that the majority of petitioner's fibrosis on biopsy (75-80%) can be attributed to a condition (fatty liver disease) that neither his biopsy nor medical records support as a diagnosis for this petitioner. (*Id*. at 8.) He charges that the assertion has no scientific underpinning. (*Id*.) Moreover, Dr. Gish does not address Dr. Lammert's assessment of the grade 3 inflammation. (*Id*.) In response to Dr. Gish's assertion that there should have been greater fibrosis if the condition were chronic, Dr. Lammert indicates "[t]here is no literature that firmly establishes or codifies the expected progression of fibrosis in AIH that is untreated." (*Id*.)

6. Dr. Gish's second report and Dr. Lammert's responsive (fourth) report

With regard to petitioner's pre-vaccination symptoms, Dr. Gish stresses that petitioner was in below-average health. Thus, he challenges Dr. Lammert's reliance on

[18] Dr. Gish indicated that "[i]n [petitioner's] case, the fat that was most likely present during his adult life may not have been present on biopsy due to his recent severe liver injury due to AIH onset following vaccination." (Ex. 105, p. 10.) However, Dr. Lammert counters that Dr. Gish has provided no evidence or scientific reasoning to support that assertion. (Ex. I, p. 7.)

typicality. (Ex. 122, pp. 6-7.) He reiterates that the symptoms at issue were nonspecific. He charges that "it is unscientific to conclude that a patient had AIH at a given time just because he presented with nonspecific symptoms. The fact that the patient subsequently developed AIH is irrelevant because the fact remains that there is no way of proving, or even reasonably suggesting, that earlier symptoms such as dizziness had anything to do with the disease." (*Id*. at 7.) With regard to the pre-vaccination ALT result, Dr. Gish counters that nonalcoholic fatty liver disease is far more common than AIH "by many magnitudes" and, therefore, "an abnormal ALT result is far more likely to indicate [nonalcoholic fatty liver disease] than it is to indicate AIH." (*Id*.) Regarding the biopsy results, Dr. Gish indicates that petitioner's biopsy was taken using a 20-gauge needle. He asserts that a 20-gauge needle is adequate to test for AIH, but not a fatty liver. A 16-gauge needle would be more appropriate to screen for a variety of conditions. (*Id*. at 8-9.)

Dr. Lammert contends that Dr. Gish's suggestion of a fatty liver disease to explain the ALT result is not supported because the later biopsy did confirm AIH but not fatty liver. (Ex. J, p. 2.) Dr. Lammert does not specifically address the question of needle gauge, but indicates the biopsy should not be viewed as a false negative for a fatty liver because no other imaging completed in the case has shown steatosis. (*Id*.) He further suggests his opinion with respect to the chronicity of the AIH confirmed by the biopsy is supported by the finding of stage one fibrosis. (*Id*.)

VI. Discussion

a. *Althen* prong one

Under *Althen* prong one, petitioner must provide a "reputable medical theory," demonstrating that the vaccine received can cause the type of injury alleged. *Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1355-56 (Fed. Cir. 2006) (citations omitted). Such a theory must only be "legally probable, not medically or scientifically certain." *Knudsen*, 35 F.3d at 549. Petitioner may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu*, 569 F.3d at 1378-79 (citing *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1325-26 (Fed. Cir. 2006)). However, "[a] petitioner must provide a 'reputable medical or scientific explanation' for [her] theory. While it does not require medical or scientific certainty, it must still be 'sound and reliable.'" *Boatmon*, 941 F.3d at 1359 (quoting *Knudsen*, 35 F.3d at 548-49). Here, for the reasons discussed below, I conclude that petitioner has not come forward with sufficient evidence to preponderantly support his theory under *Althen* prong one.[19]

[19] In 2011, a series of cases alleging that the hepatitis B vaccine caused AIH were collected by one special master and adjudicated collectively. The special master denied entitlement to compensation, including a finding that petitioner's theory was not adequately supported under *Althen* prong one. Two of those cases had subsequent appellate history. Initially, the Court of Federal Claims reversed; however, the Federal Circuit ultimately reinstated and affirmed the special master's conclusion. *Porter v. Sec'y of Health & Human Servs*., 663 F.3d 1242 (Fed. Cir. 2011). One subsequent decision by a different special master found a petitioner entitled to compensation for acute hepatitis caused by a Flumist vaccination.

Petitioner presents two different experts with two overlapping, but ultimately different, approaches to theorizing that the hepatitis B vaccine can cause AIH. Dr. Gish theorizes that components of the vaccine at issue can cross react with cells of the liver to result in autoimmune attack. (Ex. 105, p. 5.) He seeks to support his theory circumstantially by relying on his own prior clinical experience that suggests hepatitis B infection can cause AIH, the ability of the hepatitis B vaccine to cause other autoimmune conditions, and case reports implicating the hepatitis A vaccine as a cause of AIH in particular. All of this, he suggests, "sets the stage" for the hepatitis B vaccine to be capable of causing AIH. (*Id*. at 6.) Dr. Gershwin highlights some of the same points, but by contrast, disclaims any need to identify a relevant structural homology and cross-reaction between the vaccination and liver tissue. (Ex. 14, p. 7; Ex. 78, p. 2.) Instead, he relies on the liver-trophic nature of the hepatitis B virus, a mouse model that shows AIH to be initiated by innate immunity and resulting inflammation, and his own assertion that vaccine-caused inflammation may cause somatic hypermutation. This, he opines, results in neoantigens within the liver that can then lead to autoimmune attack of the liver. (Ex. 14, pp. 7-8.) Neither of these approaches is supported by sound and reliable scientific explanation.

"Hepatitis" refers broadly to inflammation of the liver.[20] Hepatitis "A," "B," and "C" refer to three distinct viral diseases that can affect the liver caused by viruses of the same names. Whereas hepatitis A is generally self-limited, hepatitis B and C can both become chronic.[21] The risk of liver-related complications due to hepatitis B infection is variable. For example, only 8-20% of untreated adults develop cirrhosis[22] within five years. (Terrault, et al., *AASLD Guidelines for Treatment of Chronic Hepatitis B*, 63 HEPATITIS 1 (2016) (Ex. D, Tab 1, p. 3).) "Autoimmune hepatitis" or "AIH" is a specific

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Agnew v. Sec'y of Health & Human Servs., No. 12-551V, 2016 WL 1612853 (Fed. Cl. Spec. Mstr. Mar. 30, 2016). Otherwise, compensation for autoimmune hepatitis has since been limited to the context of settlement, though not in any case where the hepatitis B vaccine was solely at issue.

[20] *Hepatitis*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=22189&searchterm=hepatitis (last visited June 2, 2023).

[21] *Compare Hepatitis A*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=80603&searchterm=hepatitis+A (last visited June 2, 2023) *with Hepatitis B*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=80611&searchterm=hepatitis+B (last visited June 2, 2023) *and Hepatitis C,* DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=80612&searchterm=hepatitis+C (last visited June 2, 2023).

[22] Cirrhosis refers to any of a group of chronic diseases of the liver characterized by loss of normal lobular architecture with fibrosis, and by destruction of parenchymal cells and their regeneration to form nodules. These diseases have long latent periods, usually followed by sudden abdominal swelling and pain, hematemesis, dependent edema, or jaundice. In advanced stages, prominent symptoms include ascites, jaundice, portal hypertension, and central nervous system disorders that may end in hepatic coma. Often informally called cirrhosis of the liver despite the redundancy. *Cirrhosis*, DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=9929 (last visited June 2, 2023).

form of chronic liver inflammation that is believed to be autoimmune largely due to its association with autoantibodies. (Albert J. Czaja, *Transitioning from Idiopathic to Explainable Autoimmune Hepatitis*, 60 DIG DIS SCI 2881 (2015) (Ex. 16, p. 1); Maya, et al., *supra*, at Ex. 115, p. 11.) As both parties' experts agree, the cause(s) of AIH are unknown. (Ex. 14, pp. 3, 6; Ex. B, p. 4; Ex. D, pp. 6-7.)

Prior case reports have suggested that some instances of AIH may have followed infection by multiple viruses, including all three hepatitis viruses. (Czaja, *supra*, at Ex. 16, p. 6; Lohse, et al., *EASL Clinical Practice Guidelines: Autoimmune hepatitis*, 63 JOURNAL OF HEPATOLOGY 971 (2015) (Ex. D, Tab 2, p. 6).) However, the relationship between viral infection and AIH remains unclear. (Lohse, et al., *supra*, at Ex. D, Tab 2, p. 6.) For example, while the hepatitis C virus has been associated with the antibodies characteristic of type 2 AIH (discussed further below), it is still not considered "an important cause" of type 2 AIH due to additional differences. (Albert J. Czaja, *Autoimmune Hepatitis, Evolving Concepts and Treatment Strategies*, 40 DIG DIS SCI 435 (1995) (Ex. 17, p. 9).) In fact, clinical practice guidelines treat hepatitis infection and AIH as mutually exclusive, specifically instructing that chronic hepatitis B or C infection should be ruled out before AIH is diagnosed. (Lohse, et al., *supra*, at Ex. D, Tab 2, p. 3 (Table 3).)

In any event, Dr. Gershwin confirms in his first report that no etiologic role has been evidenced for any of the hepatotropic viruses in causing AIH. (Ex. 14, p. 6 (quoting Van Gemeren, et al., *supra*, at Ex. 68, p. 4).) In his final report, he further confirmed there is inadequate evidence to determine that hepatitis B specifically is a cause of AIH. (Ex. 136, p 1.) Thus, although Dr. Gish cites his own anecdotal clinical experience with five patients as evidence linking hepatitis B infection with AIH (Ex. 122, p. 5), the evidence of record does not preponderate in favor of the conclusion that the hepatitis B virus is an established cause of AIH. Had this been the case, then Dr. Gershwin suggested it would have strengthened the case for invocation of molecular mimicry. (Ex. 136, p. 2.)

There are also some case reports referenced within the medical literature that purport to link the hepatitis B vaccine to AIH. (Van Gemeren, et al., *supra*, at Ex. 68.) However, these isolated reports are in contrast to the standard of care for AIH, which provides that patients suffering AIH should be vaccinated against hepatitis B. (Ex. D, p. 2; Lohse, et al., *supra*, at Ex. D, Tab 2, pp. 24-25; Ex. A.) According to Dr. Lammert, this standard of care strongly suggests that hepatitis B vaccine is not viewed in the relevant medical community as likely to cause adverse effects in AIH patients. (Ex. D, p. 2.) Nonetheless, "'the fact that case reports can by their nature only present indicia of causation does not deprive them of all evidentiary weight.'" *Paluck v. Sec'y of Health & Human Servs.,* 104 Fed. Cl. 457, 475 (2012) (quoting *Campbell v. Sec'y of Health & Human Servs.*, 97 Fed. Cl. 650, 668 (2011), *aff'd* 786 F.3d 1373 (Fed. Cir. 2015)). However, upon review of the specific case reports filed in this case, they are not persuasive as evidence supporting petitioner's theory. In particular, none of the case reports isolates the hepatitis B vaccine. The majority of case reports involve the hepatitis A vaccine alone. Only two include the hepatitis B vaccine, but those two case

reports additionally included hepatitis A vaccination. (*See* Van Gemeren, et al., *supra*, at Ex. 68, p. 5 (Table 1).)

The three hepatitis viruses are structurally different and are not interchangeable. (*E.g*. Zignego, et al., *HBV and HCV chronic infection: Autoimmune manifestations and lymphoproliferation*, 8 AUTOIMMUNITY REVS 107 (2008) (Ex. 23, p. 1); Tabak, et al., *Autoimmune hepatitis induced by the prolonged hepatitis A virus infection*, 7 ANNALS OF HEPATOLOGY 177 (2008) (Ex . 30, p. 1); *see also* Van Gemeren, et al., *supra*, at Ex. 68, p. 4; Czaja, *supra*, at Ex. 17, p. 14.) Additionally, Dr. Lammert further explains that the hepatitis A and B vaccines are formulated differently, with the hepatitis A vaccine using an inactivated virus and the hepatitis B vaccine using a non-infectious subunit derived from surface antigen. (Ex. I, p. 5.) Dr. Gish acknowledges the distinction, but argues it is irrelevant because both vaccines ultimately rely on epitope stimulation. (Ex. 122, pp. 4-5.) However, Dr. MacGinnitie explains relative to comparing the hepatitis B vaccine and wild virus that the use of a single protein surface antigen in the hepatitis B vaccine reduces the potential for molecular mimicry, which is the mechanism of autoimmunity suggested by Dr. Gish's reliance on cross reactivity between vaccine components and liver tissue. (Ex. K, p. 2; Ex. 105, p. 5.) This suggests at least one way in which the different vaccine formulations could be meaningful. Dr. Gish merely assumes without substantiation that the difference in vaccine formulation has no significance. On the whole, Dr. Gish is not persuasive in opining that evidence relating to the hepatitis A vaccine is helpful in determining whether the hepatitis B vaccine can cause AIH.

Importantly, although AIH is characterized by the presence of autoantibodies, the significance of those autoantibodies is not uniform. There are two types of AIH associated with different types of autoantibodies.[23] Type 1 AIH is associated with antinuclear antibodies ("ANA") and smooth muscle antibodies ("SMA"). Type 2 AIH is associated with antibodies to liver kidney microsome type 1 ("anti-LKM1"). (Czaja, *supra*, at Ex. 16, pp. 1-2.) The antibodies associated with each type of AIH are generally mutually exclusive and each type has distinct genetic predispositions recognized. (*Id*. at 2.) Type 1 AIH is 20-times more common than type 2 AIH, with type 2 mainly affecting children of European descent. (Maya, et al., *supra*, at Ex. 115, p. 11; Czaja, *supra*, at Ex. 16, p. 2.) An antigenic target (CYP2D6) for autoimmunity has been discovered for type 2 AIH, but not type 1. (Czaja, *supra*, at Ex. 16, p. 2.) Other antigens have been implicated in both type 1 and type 2 AIH, including six autoantigens in type 1 AIH, but none have been identified as pathogenic. (*Id*. at 6.) Thus, although autoantibodies are a hallmark of AIH, they have been useful only in identifying the antigen target for type 2 AIH. For type 1 AIH, "[t]heir diversity, lack of disease specificity, and non-pathogenicity in type 1 [AIH] suggest that the currently recognized autoantibodies are not markers of the pivotal autoantigen." (*Id*.)

All of this leaves petitioner's reliance on analogy to other types of autoimmunity unpersuasive. As explained above, the type of AIH that demonstrates a broader presence of autoantibodies that could also be implicated in other autoimmune conditions (*i.e.* type 1) is the type of AIH for which the significance of these

[23] More specific subcategories have also been proposed. (Czaja, *supra*, at Ex. 17.)

autoantibodies remains unknown and not necessarily pathogenic. Dr. Gish's specific suggestion that the hepatitis B vaccine may cause AIH via molecular mimicry because hepatitis B vaccine antigen may cross react with liver cells is speculative and entirely unsupported given that the antigenic target and pathologic autoantigen has not been identified for type 1 AIH. (Ex. 105, p. 5.) Even assuming *arguendo* that the hepatitis B vaccine can cause autoimmune damage to other body tissues (this point is disputed by respondent), this still would not in itself be strong evidence that it can cause autoimmune damage to liver tissue in particular. The idea that the hepatitis B vaccine can cause AIH is not otherwise supported. (Ex. 105, p. 6 (Dr. Gish agreeing there are no cases of AIH following hepatitis B vaccine reported in the literature).)

The remaining question then is whether Dr. Gershwin has nonetheless presented a sound and reliable explanation supporting his theory without relying on any demonstrable cross reaction between vaccine components and liver tissue. Dr. Gershwin appears to be on reasonably sound footing in his broader assertion that AIH may have an innate inflammatory component and ultimately involve a T-cell mediated response. However, Dr. Gershwin offers no specific support for the idea that vaccination would lead to inflammation preferentially targeting the liver. Nor does he support his contention that this would result in somatic hypermutation. Nor does he provide support for his combining of these two ideas to contend that somatic hypermutation would mimic the mechanism of neoantigens as seen in drug-induced AIH. On the whole, Dr. MacGinnitie is persuasive in suggesting Dr. Gershwin's theory as presented is ultimately too vague to be testable and, therefore, not scientifically sound or reliable. (Ex. F, p. 2.)

The "neoantigen" concept Dr. Gershwin relies upon appears to derive from the context of drug-induced AIH. In that context, it is theorized that drug components entering the liver may generate neoantigens as a result of metabolization of the drug which then provokes an immune response. (Ian R. Mackay, *Hepatoimmunology: A perspective*, 80 IMM CELL BIO 36 (2002) (Ex. 70, p. 3); Floreani, et al., *Etiopathogenesis of autoimmune hepatitis*, 95 J OF AUTOIMMUNITY 133 (2018) (Ex. 79, p. 7); Urs Christen and Edith Hintermann, *An Update on Animal Models of Autoimmune Hepatitis: Are We There Yet?*, 21 CURRENT PHARMA DESIGN 2391 (2015) (Ex. 90, p. 5); Francque, et al., *Epidemiology and treatment of autoimmune hepatitis*, 4 HEPATIC MEDICINE: EVID AND RESEARCH 1 (2012) (Ex. 125, p. 2).) Here, however, Dr. Gershwin proposes an entirely different mechanism of autoinflammation rather than metabolization as the source for neoantigens. Extension of the neoantigen concept to autoinflammation is not supported on this record. Based on my review of the literature filed by petitioner, the only context (apart from drug-induced AIH) in which neoantigens are discussed is as part of a transgenic animal model for AIH, where neoantigens are used in an experimental context to artificially provoke a break in hepatic tolerance. (Jaeckel, et al., *The benefit of animal models for autoimmune hepatitis*, 25 BEST PRAC & RES CLINICAL GASTROENTEROL 643 (2011) (Ex. 20, p. 4).) But this does not readily support the notion that autoinflammation would naturally lead to neoantigens. Rather, Dr. Gershwin's opinion appears to be based on the speculation that if neoantigens can occur in some contexts, then they can result from any substance, including vaccines. (Ex. 14, p. 7.)

Dr. Gershwin's suggestion that AIH can be induced by damaging inflammation is based on his reference to the Con-A animal model. However, Dr. MacGinnitie explains that Con-A is a far more potent immune stimulator than vaccination. (Ex. B, pp. 4-7.) Even if credited, this model merely supports a role for inflammation in the pathogenesis of AIH. (Wang, et al., *Immune mechanisms of Concanavalin A model of autoimmune hepatitis*, 18 WORLD J GASTROENTEROL 119 (2012) (Ex. 64); Jaeckel, et al., *supra*, at Ex. 20.) It does not implicate vaccination as a source of liver-specific inflammation or in any way purport to mimic the effects of vaccination. Nor is it readily apparent that it would support any of Dr. Gershwin's specific assertions regarding somatic hypermutations or neoantigens. Ultimately, even Dr. Gershwin himself suggests that the animal models he cites are not strong evidence. He indicates that the multiplicity of differing animal models support multiple potential immune pathways to autoimmune attack on the liver and that, as a whole, they demonstrate that it is "virtually impossible" to design a mouse model of AIH. (Ex. 78, p. 3.) This is especially problematic given the paucity of evidence that hepatitis B vaccine in particular causes AIH in humans.

Considering all of this collectively and in the context of the record as a whole, I conclude that petitioner has not preponderantly established that the hepatitis B vaccine can cause AIH.

b. *Althen* prong two

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326; *Grant*, 956 F.2d at 1148. In establishing that a vaccine "did cause" injury, the opinions and views of the injured party's treating physicians are entitled to some weight. *Andreu*, 569 F.3d at 1367; *Capizzano*, 440 F.3d at 1326 (quoting *Althen*, 418 F.3d at 1280) (stating that "medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury'"). However, medical records and/or statements of a treating physician's views do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. *See* Section 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 746 n.67 (2009) (stating that "there is nothing . . . that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted"). Ultimately, petitioner may support his claim either through his medical records or by expert opinion. § 300aa-13(a)(1).

In this case, petitioner does not point to any treating physician opinion that supports his claim. (ECF No. 98-1, pp. 18-23.) Indeed, petitioner's treating hepatologist, Dr. Shiffman, has provided a letter confirming his view that vaccination against hepatitis B is an "appropriate treatment" for patients with AIH. (Ex. A, p. 2.) "A treating physician's decision to administer or withhold a vaccination can be highly

probative of causation." *Tarsell v. United States*, 133 Fed Cl. 782, 797 (2017) (citing *Andreu,* 569 F.3d at 1376).) In this particular case, Dr. Shiffman did not administer a hepatitis B vaccine to petitioner because he confirmed that he was already vaccinated against hepatitis B; however, he explicitly indicated that "[s]ince autoimmune hepatitis is a chronic liver disease vaccination for hepatitis B is indicated for [petitioner]." (Ex. A, p. 2.) This is more consistent with Dr. Lammert's stated view regarding the standard of care for AIH, and whether vaccination can cause or exacerbate AIH, than it is Dr. Gershwin and Dr. Gish's competing opinions. (*Compare* Ex. D, pp. 4, 6 and Ex. 14, p. 8.) No other treating physician has provided any opinion either supporting or refuting vaccine causation. Thus, the remaining question is whether Drs. Gershwin and Gish are otherwise persuasive in suggesting there is a logical sequence of cause-and-effect implicating petitioner's hepatitis B vaccine in the development of his AIH. They are not.

Dr. Gershwin and Dr. Gish are unpersuasive in seeking to rely simply on the mere notion of a post-vaccination onset to establish causation-in-fact. Dr. Gershwin's assessment of specific causation relies primarily on the assertions that "it is more likely that the clinical course began shortly after immunization" and that "[t]here are no other antecedent environmental challenges" that would lead to an autoimmune phenomenon. (Ex. 14, pp. 4, 8.) Dr. Gish similarly opined. He premised his opinion on the idea that there is a "striking" temporal relationship between petitioner's vaccination and the onset of his AIH that evidences causation in the absence of any other infection or environmental insult to explain his symptoms. (Ex. 105, p. 10.) Little else is offered by way of any supporting evidence or rationale. However, without more, this is not persuasive as a means to assert vaccine causation. *See e.g., Devonshire v. Sec'y of Health and Human Servs.,* No. 99-031V, 2006 WL 2970418, at *19 (Fed. Cl. Spec. Mstr. Sept. 28, 2006) (noting that a medical expert's "*post hoc ergo proptor hoc* reasoning…has been consistently rejected by the Court and is 'regarded as neither good logic nor good law'") (quoting *Fricano v. U.S.,* 22 Cl. Ct. 796, 800 (1991) (emphasis in original)). The Federal Circuit has specifically explained that "neither a mere showing of a proximate temporal relationship between vaccination and injury, nor a simplistic elimination of other potential causes of the injury suffices, without more, to meet the burden of showing actual causation." *Althen*, 418 F.3d at 1278 (citing *Grant*, 956 F.2d at 1149).

Moreover, the temporal relationship Dr. Gish relies upon is not "striking" when juxtaposed with Dr. Gershwin's actual medical theory. Both Dr. Gershwin and Dr. Gish suggest that onset of petitioner's AIH symptoms occurred about one-month post-vaccination. (Ex. 14, p. 4; Ex. 105, p. 10.) However, whereas Dr. Gish stresses the "sudden and rapid" onset of symptoms occurring at that time (Ex. 122, p. 3), Dr. Gershwin specifically opines that his theory contemplates an initial innate immune response occurring "within a very short period of time, in theory within hours." (Ex. 14, p. 8.) He explains that "[t]his innate immune response is a characteristic feature of the etiology of autoimmune hepatitis." (*Id*.) Thus, Dr. Gershwin indicates that petitioner's clinical course actually began "shortly after the immunization." (*Id*. at 4.) In that regard, Dr. Gershwin provides an extensive quotation from Van Gemeren, et al., which explains that "[c]linical manifestations are heterogeneous and vary from no symptoms to

fulminant hepatic failure and often follow a spontaneous fluctuating course. AIH can have a subclinical course for a long time." (Ex. 14, p. 6 (quoting Van Gemeren et al, *Supra*, at (Ex. 68, p. 3).) Dr. Gershwin indicates that this discussion "is consistent with the opinions I have expressed herein and with the progression of [petitioner's] illness." (*Id*.) Dr. Gish likewise acknowledges that AIH can present heterogeneously and further explains that "it is often difficult to say with certainty when a condition characterized by a variety of non-specific symptoms actually began." (Ex. 105, p. 8.)

That is, Dr. Gershwin confirms that the "striking" onset of symptoms occurring one-month post-vaccination does *not* herald the immune response at issue and both of petitioner's experts further explain that the true onset of AIH is generally difficult, if not impossible, to determine. Moreover, Dr. Gershwin specifically contemplates at least some period of subclinical disease process is *required* in order to marry his theory to the facts of this particular case. However, neither expert explains why, apart from their own willingness to implicate the vaccination, this necessary subclinical period should be assumed to have started just after vaccination but no earlier. Neither expert points to any sign, symptom, or characteristic of AIH that would indicate, even circumstantially, that petitioner's AIH was likely to have begun around that specific time given petitioner's own medical history. Therefore, petitioner's reliance on a temporal association between vaccination and injury is speculative and unpersuasive even before reaching any of the particular complications raised by Dr. Lammer's competing opinion.

Additionally, Dr. Gish specifically predicates his causal assessment on the assumption that preexisting AIH is "ruled out." (Ex. 105, p. 10.) However, even accepting the remainder of Dr. Gish's contentions *arguendo*, this would still dramatically overstate what his reports establish. While Dr. Gish reasonably explains that it is impossible to say definitively whether petitioner's pre-vaccination symptoms were manifestations of AIH, Dr. Lammert is more persuasive on the whole in asserting that there is substantial reason to conclude that petitioner's AIH was more likely to have been chronic. Consistent with both Dr. Gershwin and Dr. Gish's descriptions of the general course of AIH, Dr. Lammert opines that "[t]he evolution of [petitioner's] disease is compatible with an expected trajectory of AIH as patients with AIH may harbor chronic 'smoldering' inflammation for months-years prior to diagnosis." (Ex. G, p. 4.)

The record of this case presents two conflicting expert hepatology opinions regarding the degree of fibrosis on biopsy that would confirm a chronic course of AIH. (*Compare* Ex. D, p. 6 (Dr. Lammert opining any degree of fibrosis indicates a period of subclinical disease *and* Ex. 105, p. 10 (Dr. Gish opining that stage 2 fibrosis, but not stage 1 fibrosis, indicates a chronic course of AIH).) In that regard, Dr. Lammert explains there is no firm guidance in the literature with respect to this question. (Ex. I, p. 8.) However, both experts agree that firsthand review of the fixed biopsy tissue is preferred when rendering a final diagnostic conclusion. (Ex. 105, pp. 9-10; Ex. I, p. 8.) Importantly then, the reviewing pathologist determined petitioner's biopsy diagnosed "chronic" hepatitis. (Ex. 4, p. 228.) Dr. Gish further opines that "when assessing liver biopsies it is extremely important to analyze the quality of the biopsy." (Ex. 122, p. 8.) Here too, petitioner's treating hepatologist, Dr. Shiffman, documented that he

additionally reviewed the biopsy slides and, although he found the specimen "adequate," he expressed concern that the degree of fibrosis may be underestimated due to fragmentation. (Ex. 5, p. 34.) All of this first-hand observation is better aligned with Dr. Lammert's interpretation of the biopsy result than Dr. Gish's.

Furthermore, Dr. Gish bases his assessment of the biopsy in part on his determination that a substantial percentage (in fact, the majority) of the fibrosis confirmed on biopsy should be attributed to nonalcoholic fatty liver disease. (Ex. 105, pp. 3, 10.) However, petitioner's biopsy result specifically confirms that nonalcoholic fatty liver disease was not present. (Ex. 4, p. 228.) And, in any event, petitioner has never been diagnosed with that condition and, regardless of whether the biopsy itself was likely to detect it, Dr. Lammert is persuasive in noting that petitioner had other imaging that likewise did not detect a fatty liver. (Ex. I, p. 7.) Specifically, petitioner's liver was assessed as normal or unremarkable after both ultrasound and CT scan. (Ex. 6, pp. 229, 235; Ex. 57, p. 53.) Thus, Dr. Gish's opinion regarding the biopsy is less persuasive given that it is based in part on a factual assumption (the presence of fatty liver disease) that is not supported by preponderant evidence. *Burns v. Sec'y of Health & Human Servs.*, 3 F. 3d 415 (Fed. Cir. 1993) (holding that "[t]he special master concluded that the expert based his opinion on facts not substantiated by the record. As a result, the special master properly rejected the testimony of petitioner's medical expert."); *see also Rickett v. Sec'y of Health & Human Servs.,* 468 Fed. Appx. 952, 958 (Fed. Cir. 2011) (holding that "it was not error for the Special Master to assign less weight to Dr. Bellanti's conclusion regarding challenge-rechallenge to the extent it hinged upon Mr. Rickett's testimony that was inconsistent with the medical records."); *Dobrydnev v. Sec'y of Health & Human Servs.,* 566 Fed. Appx. 976, 982–83 (Fed. Cir. 2014) (holding that the special master was correct in noting that "when an expert assumes facts that are not supported by a preponderance of the evidence, a finder of fact may properly reject the expert's opinion").

Petitioner's pre-vaccination symptoms, acknowledged by all to be non-specific, and the isolated February 2015 finding of elevated ALT, are less helpful in resolving this case precisely because of the limitations raised by Dr. Gish. In particular, Dr. Lammert's suggestion that petitioner sought care from the emergency department more than would be typical must be weighed against the fact that petitioner appears to have used the emergency department in lieu of regular primary care. Moreover, he received specific diagnoses at the time. (Ex. 2, pp. 6, 10, 13, 22, 31-37; Ex. 6, pp. 337, 677; Ex. 7, pp. 3, 11, 21.) Thus, the question of onset does *not* turn on the prior nonspecific symptoms alone. However, in combination with Dr. Lammert's more persuasive interpretation of the biopsy, they do have the potential to lend further support to Dr. Lammert's overall view of the clinical history.

To the extent Dr. Gish is interpreted as opining that petitioner's prior non-specific symptoms and isolated ALT elevation are not sufficient to *diagnose* AIH, he is clearly correct. But that is not the issue that Dr. Lammert's competing opinion presents. There is no debate in this case that petitioner was ultimately correctly diagnosed with AIH. The question is how to view the preceding non-specific symptoms and elevated ALT

result in light of petitioner's overall clinical history, which includes a later confirmed AIH diagnosis. *Accord R.K. v. Sec'y of Health & Human Servs*., No. 03-632V, 2015 WL 10936124, at *67 (Fed Cl. Spec. Mstr. Sept. 28, 2015) (finding respondent's expert persuasive in establishing onset of autism well before the condition was ultimately recognized by clinicians in part because "there is a difference between engaging in diagnosis and recognizing with the benefit of hindsight that certain signs or symptoms are indicative of a subsequently diagnoses condition"), *mot. rev. den'd*, 125 Fed CL. 57 (2016), *aff'd* 671 F. App'x 792 (Fed. Cir. 2016). The crux of the experts' disagreement is Dr. Gish's assertion that "it is unscientific to conclude that a patient had AIH at a given time just because he presented with nonspecific symptoms. The fact that the patient subsequently developed AIH is irrelevant . . ." (Ex. 122, p. 7.) Dr. Gish further suggests that nonalcoholic fatty liver disease should be considered a more likely explanation for petitioner's non-specific symptoms and elevated ALT because it is, in general, "far more common" than AIH. (*Id*.) Neither of these points is persuasive.

Dr. Gish provides no support for his suggestion that it is improper to view a patient's clinical history holistically. Even if Dr. Gish is correct to stress the limitations of the available data points, referring to a subsequently confirmed diagnosis as entirely "irrelevant" likely goes too far. Even with caveats, Dr. Gish does not disagree that at least some of petitioner's non-specific symptoms are consistent with AIH, that elevated ALT is consistent with AIH, and that AIH can initially present as a collection of non-specific symptoms. Additionally, the fact that fatty liver disease is generally more common than AIH is of no relevance where petitioner has already been diagnosed with the rarer condition. Dr. Lammert is attributing non-specific symptoms and an isolated lab result to a condition petitioner is confirmed to suffer while Dr. Gish is, at least in part, hypothesizing that a different, undiagnosed, condition is a more likely cause of the same ALT lab result. Dr. Gish's assessment of fatty liver disease has less tether to petitioner's own medical history no matter how common that alternative diagnosis is in the general population. And, in any event, all of these uncertainties cut both ways, remaining a far cry from actually *ruling out* preexisting AIH as Dr. Gish asserts.

There is some additional suggestion from petitioner's experts that, even if petitioner did have preexisting AIH, then it would still be reasonable to conclude that the vaccination significantly aggravated the condition. However, the basis for this alternative suggestion has not been adequately explained, especially given the degree to which his experts have otherwise advocated for an initial post-vaccination onset. And, in any event, considering the expert reports as a whole, this alternative suggestion of significant aggravation would still necessarily rely on the same unpersuasive assessment of temporality as discussed above.

c. *Althen* prong three

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a

timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id.* at 1352; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 503 Fed. Appx. 952 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Human Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

Here, petitioner's claim fails under *Althen* prong three for the same reasons described relative to *Althen* prong two. Although petitioner clearly experienced new symptoms of AIH about 30 days post-vaccination, petitioner has not preponderantly established that this is when his AIH first began. Instead, respondent is more persuasive in suggesting that petitioner had chronic, smoldering AIH that predated his vaccination. And, in any event, even if petitioner's condition did first outwardly manifest 30 days post-vaccination, that onset period is not in itself consistent with Dr. Gershwin's theory of causation, which contemplates an innate immune response commencing within hours of vaccination. Dr. Gershwin's theory requires that a course of subclinical disease preceded symptom onset. However, there is no evidence to suggest that this proposed course of subclinical AIH began within hours of petitioner's vaccination.

VII. Conclusion

Petitioner has clearly suffered and he has my sympathy. Moreover, given all of the above, it is understandable that he would come to personally believe that his condition was caused by his hepatitis B vaccination. However, for all the reasons discussed herein, petitioner has not preponderantly demonstrated that he actually suffered a vaccine-caused injury and is therefore not entitled to compensation. Accordingly, this case is dismissed.[24]

IT IS SO ORDERED.

s/Daniel T. Horner
Daniel T. Horner
Special Master

[24] In the absence of a timely-filed motion for review of this Decision, the Clerk of the Court shall enter judgment accordingly.